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Published:

with international search report

[Continued on next page]

(54) Title: MORPHOLINE DERIVATIVES AND INTERMEDIATES THEREFOR

(57) Abstract: Compound of formula (I); which is;3-({[({[(2S)-4-(3,4-dichloroben-zyl)morpholin-2-yl]methyl}amino)carbonyl]--amino}methyl)-N-ethylbenzamide;and salts and solvates thereof, a process for its preparation, pharmaceutical formulations containing it and its use in therapy.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D265/30 C07C229/60 C07C215/18 A61K31/5375 A61P29/00

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

PO-Tn	ternal, CHEM ABS Data		
_,	50, har, 6,121, 1,55 - 5,55		
. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.
A	WO 98 56771 A (SCHERING AG) 17 December 1998 (1998-12-17) cited in the application claims 1,31-34		1,3-5
X	SARTORI E ET AL: "SYNTHESIS AN ACTIVITIES OF NET ARYLSULFONAMI THROMBOXANE A2 RECEPTOR ANTAGON EUROPEAN JOURNAL OF MEDICINAL CEDITIONS SCIENTIFIQUE ELSEVIER, vol. 28, no. 7/8, 1993, pages 6 XP000396678 ISSN: 0223-5234 cited in the application page 631, left-hand column, lin "methyl 3-aminomethyl benzoate"	9	
X Fur	ther documents are listed in the continuation of box C.	Y Pätent family members are listed	In annex.
Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'B' document published prior to the international filing date but , are later than the priority date claimed		 "T" later document published after the International filing date or priority date and not in conflict with the application but afted to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family 	
Date of the	e actual completion of the international search	Date of mailing of the international se	arch report
6 October 2003		15/10/2003	
Name and	mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2 NL – 2280 HV Rijswljk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Hass, C	



PCT/EP 03/03338

		PC1/EP 03/03338
C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category ^a	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 31431 A (NISSHIN FLOUR MILLING CO; KIKUCHI HARUHIKO (JP); SATOH HIROAKI (JP) 23 November 1995 (1995-11-23) page 28, line 21 - line 24 page 35, line 20 - line 23 page 41, line 5	1,2,6-8, 10
A	EP 0 243 959 A (DAINIPPON PHARMACEUTICAL CO) 4 November 1987 (1987-11-04) page 43, example 24	1,10
A	WO 95 31442 A (NISSHIN FLOUR MILLING CO; KIKUCHI HARUHIKO (JP); SATOH HIROAKI (JP) 23 November 1995 (1995-11-23) page 40, line 6 - line 10 page 42, line 2 - line 4 page 43, line 5	10-12
A,P	WO 02 26723 A (HARRISON LEE ANDREW; JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) claims 1,11,12,14,17-23,25,26; examples	1-8,10



INTERNATIONAL SEARCH REPORT

interponal application No. PCT/EP 03/0338

Box I Observations where certain claims wer found unsearchable (Continuation of it m 1 of first sheet)	
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.	
Clálm's Nds::* because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:	
a Chalma Nica	
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple Inventions in this International application, as follows:	
As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims.	
2. As all searchable daims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	
As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:	
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:	
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.	

Internation Discation None v.
PCT/EF 03/03338

			101721	
Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9856771 A	17-12-1998	US AT	6207665 B1 232522 T	27-03-2001 15-02-2003
		AU	735462 B2	12-07-2001
		AU	8625898 A	30-12-1998
		DE	69811363 D1	20-03-2003
		DK	988292 T3	22-04-2003
		EE	9900565 A	15-06-2000
		EE	200200682 A	15-04-2003
		EE EE	200200683 A 200200684 A	15-04-2003 15-04-2003
		₩ 0	200200064 A 9956771 A2	17~12~1 9 08~
		EP	1254899 A2	06-11-2002
		ĒΡ	0988292 A2	29-03-2000
		ĒS	2191320 T3	01-09-2003
		HU	0003929 A2	28-05-2001
		JP	2002503239 T	29-01-2002
		NO	996068 A	11-02-2000
		NO	20031373 A	11-02-2000
		PL	337758 A1	11-09-2000
		SK	171399 A3	12-09-2000 21-06-2000
		TR US	9903034 T2 2003158205 A1	21-08-2003
		US	2003138205 A1 2003139425 A1	24-07-2003
		บร	6541476 B1	01-04-2003
		US	6534509 B1	18-03-2003
		US	6573266 B1	03-06-2003
_		US	2002177598 A1	28-11-2002
WO 9531431 A	23-11-1995	BR	9507892 A	18-11-1997
		CA	2189964 A1	23-11-1995
		DE	69527786 D1	19-09-2002 10-04-2003
		DE Ep	69527786 T2 0760362 A1	05-03-1997
		WO	9531431 A1	23-11-1995
		US	5753654 A	19-05-1998
EP 0243959 A	04-11-1987	AT	79616 T	15-09-1992
		AU	592177 B2	04-01-1990
		AU	7227587 A	05-11-1987
		CA	1291135 C	22-10-1991
		CZ	8702897 A3	11-11-1998
İ		DD DE	256325 A5 3781195 D1	04 - 05-1988 24 - 09-1992
		DE	3781195 T2	18-02-1993
		DK	218787 A	31-10-1987
1		EP	0243959 A1	04-11-1987
		ËS	2043617 T3	01-01-1994
		FΙ	871828 A ,B	, 31–10–1987
		GR	3005934 T3	07-06-1993
		HK	18194 A	11-03-1994
		HU	45514 A2	28-07-1988
		HU	198193 B	28-08-1989
		JP	1686407 C 3054937 B	11-08-1992 21-08-1991
		JP JP	63264467 A	01-11-1988
		JP	2042069 A	13-02-1990
		MX	6263 A	01-11-1993
		NZ	220120 A	28-06-1989
1		147	LLUILU A	20 00 1909

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0243959	A		PH SG SK SU US	24049 A 494 G 289787 A3 1597101 A3 4870074 A	05-03-1990 15-04-1994 03-06-1998 30-09-1990 26-09-1989
			ZA KR	8703022 A 9508530 B1	20-10-1987 31-07-1995
WO 9531442	A	23-11-1995	BR CA DE DE EP ES WO US	9507666 A 2189963 A1 59511086 DL 69511086 T2 0760368 A1 2136291 T3 9531442 A1 5736550 A	23-09-1997 23-11-1995 92-09-1999 05-01-2000 05-03-1997 16-11-1999 23-11-1995 07-04-1998
WO 0226723	A	04-04-2002	AU BR CA CZ EP WO NO	9014601 A 0114321 A 2423305 A1 20031194 A3 1324991 A1 0226723 A1 20031443 A	08-04-2002 01-07-2003 04-04-2002 13-08-2003 09-07-2003 04-04-2002 26-05-2003